UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,549	01/27/2000	DANIEL HENRY DENSHAM	GJE-35	6468

23557 7590 06/05/2003

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 326066669

EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/463,549	Densham
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 13, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-17, 21, 30-34, 36, and 37* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-17, 21, 30-34, 36, and 37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Deatailed Action*

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 18, 2003 has been entered.

Specification

2. Claims 18-20 have been canceled without prejudice towards further prosecution. Claim 1 has been amended.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3-9, 15, 17, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al. (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al.

(U.S. Patent 5,620,854) (April 15, 1997) further in view of Foster (U.S. Patent 5,485,277) (January 16, 1996).

Tsien et al teach a method for sequencing a polynucleotide (Abstract), comprising the steps of :

(I) reacting a target polynucleotide with a polymerase enzyme and the different nucleotides, under conditions sufficient for the polymerase reaction (Abstract, Figures 1A, 1B and 2 and Example 3 and Claims 1-2); and

(ii) detecting an effect consequent on the incorporation of a specific nucleotide complementary to the target polynucleotide (Abstract, Claims 1, 7 and 12 and Example 4).

Tsien et al teach a method wherein the effect in step (ii) is detected by measuring radiation (Example 4).

Tsien et al teach a method wherein steps (I) and (ii) are conducted with each of the different nucleotides in turn, until incorporation is detected, and then repeated (Claims 49-50).

Tsien et al teach a method wherein step (I) is conducted with all the nucleotides present (Claim 4 and Figures 2 and 3).

Tsien et al teach a method wherein the nucleotides comprise a 3' blocking group which is removed after the polymerase reaction (Example 4 and Claims 3-5 and Figures 1-3).

Tsien et al teach a method wherein the blocking group can be selectively removed by pulsed monochromatic light (Page 25, lines 4-12).

Tsien et al teach a method wherein the nucleotide comprise a further blocking group at the terminal phosphate group of the triphosphate chain, and the further blocking group is removed prior to the removal of the 3' blocking group (Example 2).

Tsien et al inherently teach a method wherein the further blocking group can be selectively removed by pulsed monochromatic light under conditions and durations different from those required to remove the 3' blocking group (Page 25, lines 4-12).

Tsien et al inherently teach a method wherein the polynucleotide is DNA (Abstract and Figure 1).

Tsien et al do not teach a method wherein the polymerase enzyme is immobilized on a solid support.

Holzrichter et al. teach a method wherein the polymerase enzyme is immobilized on a solid support (Column 7, lines 22-28, abstract, Figure 2, and claims 1 and 11).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the polymerase enzyme immobilized on a solid support of Holzrichter et al. into the DNA sequencing method of Tsien et al , since Holzrichter et al. state, "The stationary mode of operation can be used to observe dynamic biological processes in real time and in a natural environment, such as polymerase processing of DNA for determining the sequence of a DNA molecule (Abstract, last sentence)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the polymerase enzyme immobilized on a solid support of Holzrichter et al. into the DNA sequencing method of Tsien et al. in order to

improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the polymerase enzyme immobilized on a solid support of Holzrichter et al. into the DNA sequencing method of Tsien et al., in order to achieve the express advantages noted by Holzrichter et al., of a method that provides advantages of stationary mode of operation that can be used to observe dynamic biological processes in real time and in a natural environment, such as polymerase processing of DNA for determining the sequence of a DNA molecule.

Tsien et al. in view of Holzrichter et al do not teach a nascent polynucleotide being synthesized as a result of the polymerase reaction wherein the complementary nucleotides are not labeled and the effect detected results from a conformation or mass change of the polymerase that occurs upon incorporation of the nucleotide.

Foster teaches a nascent polynucleotide being synthesized as a result of the polymerase reaction wherein the complementary nucleotides are not labeled and the effect detected results from a conformation or mass change of the polymerase that occurs upon incorporation of the nucleotide (Figure 11, Column 12, lines 30-47).This rejection is based on the fact that incorporation of a particular nucleotide in a polymerase chain reaction will occur only if it is complementary to the next nucleotide of the template strand and therefore hybridization of incorporated nucleotide would occur naturally and inherently, which is detected by surface plasmon resonance signal method of Foster. It is well known in the art to an ordinary practitioner that during an enzyme reaction, the enzyme binds to substrate to form a complex and then

dissociated to form the product, thereby inherently undergoing conformation change during the reaction. In this case, polymerase enzyme necessarily and inherently undergoes the same process, thereby attributing to configurational change. The measured product (no matter by what process it is measured) is therefore an inherent measurement of the configurational change of the enzyme during the reaction.

Tsien et al in view of Holzrichter et al. do not teach detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum.

Foster teaches the detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum (Figures 11 and 12).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a nascent polynucleotide being synthesized as a result of the polymerase reaction of Foster into the DNA sequencing method of Tsien et al in view of Holzrichter et al., since Foster states, "The secondary labeling of the target DNA or RNA is not necessary, since the binding of the target genes to the conjugate receptor, can be monitored directly by surface plasmon resonance (Column 12, lines 42-46)." By employing scientific reasoning, an ordinary artisan would have combined and substituted a nascent polynucleotide being synthesized as a result of the polymerase reaction of Foster into the DNA sequencing method of Tsien et al in view of Holzrichter et al. in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute a nascent polynucleotide being synthesized as a result of the polymerase reaction of Foster into

the DNA sequencing method of Tsien et al in view of Holzrichter et al. in order to achieve the express advantages noted by Foster, of an invention in which the secondary labeling of the target DNA or RNA is not necessary, since the binding of the target genes to the conjugate receptor, can be monitored directly by surface plasmon resonance.

5. Claim 10 is rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Foster (U.S. Patent 5,485,277) (January 16, 1996). further in view of Chang et al. (U.S. Patent 5,801,042) (September 1, 1998).

Tsien et al in view of Holzrichter et al. further in view of Foster teach the method of claims 1, 3-9, 15, 17, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. further in view of Foster do not teach the competitive inhibitor of the polymerase enzyme.

Chang et al. teach the competitive inhibitor of the polymerase enzyme (Column 24, lines 25-60).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the competitive inhibitor of the polymerase enzyme of Chang et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster, since Chang et al. state, "These nucleoside analogs act as competitive inhibitors of DNA polymerase substrates. The analogous may act as a chain terminator, cause increased lability (e.g., susceptibility to breakage) of analogue-containing DNA, and/or impair the

ability of the substituted DNA to act as template for transcription or replication (Column 24, lines 47-60)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the competitive inhibitor of the polymerase enzyme of Chang et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster in order to inhibit the DNA polymerase to control and regulate the detection of the incorporated nucleotide. An ordinary practitioner would have been motivated to combine and substitute the competitive inhibitor of the polymerase enzyme of Chang et al. into the DNA sequencing method of Tsien et al. in view of Holzrichter et al. further in view of Foster, in order to achieve the express advantages noted by Chang et al., of a competitive inhibitor of DNA polymerase substrates that may act as a chain terminator, cause increased lability (e.g., susceptibility to breakage) of analogue-containing DNA, and/or impair the ability of the substituted DNA to act as template for transcription or replication.

6. Claims 11-12 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Foster (U.S. Patent 5,485,277) (January 16, 1996). further in view of O'Donnell (U.S. Patent 6,221,642 B1) (April 24, 2001).

Tsien et al in view of Holzrichter et al. further in view of Foster teach the method of claims 1, 3-9, 15, 17, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. further in view of Foster do not teach the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide.

O'Donnell. teach the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide (Abstract , Figure 1 and Column 4, lines 26-61).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide of O'Donnell into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster, since O'Donnell states, "The beta clamp confers processivity onto the core polymerase by binding directly to the polymerase alpha subunit, thereby tethering the polymerase to DNA for processive syntheses (Column 4, lines 40-43)." O'Donnell further states, "This high degree of symmetry in the beta ring could help promote smooth gliding along the symmetrical DNA duplex (Column 4, lines 61-63)". By employing scientific reasoning, an ordinary artisan would have combined and substituted the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide of O'Donnell into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster, to improve the structure and function of the DNA polymerase. An ordinary practitioner would have been motivated to combine and substitute the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide of O'Donnell into the DNA sequencing method of Tsien et al. in view of Holzrichter et al. further in view of Foster, in order to achieve the express advantages noted by O'Donnell, of the beta clamp that confers processivity onto the core polymerase by binding directly to the polymerase alpha subunit, thereby tethering the polymerase to DNA for processive syntheses and also to achieve the advantage of the high

degree of symmetry in the beta ring that could help promote smooth gliding along the symmetrical DNA duplex.

7. Claim 13 is rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Foster (U.S. Patent 5,485,277) (January 16, 1996) further in view of Rosenthal et al. (PCT International Publication Number: WO 93/21340) (October 21, 1993).

Tsien et al in view of Holzrichter et al. further in view of Foster teach the method of claims 1, 3-9, 15, 17, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. further in view of Foster do not teach the Taq polymerase.

Rosenthal et al. teach the Taq polymerase (Page 9, lines 5-10).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Taq polymerase of Rosenthal et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster, since Rosenthal et al state, "Suitable DNA polymerases are, for example, Sequenase 2.0, T4 DNA polymerase or the Klenow fragment of DNA polymerase 1 as well as heat-stable polymerase such as Taq polymerase (for example Taquenase) (Page 9, lines 7-10)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the Taq polymerase of Rosenthal et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al.

further in view of Foster, to improve the function of the DNA polymerase. An ordinary practitioner would have been motivated to combine and substitute the Taq polymerase of Rosenthal et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster, in order to achieve the express advantages noted by Rosenthal et al., of suitable DNA polymerases for example, Sequenase 2.0, T4 DNA polymerase or the Klenow fragment of DNA polymerase 1 as well as heat-stable polymerase such as Taq polymerase (for example Taquenase).

8. Claim 14 is rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Foster (U.S. Patent 5,485,277) (January 16, 1996). further in view of Vind (U.S. Patent 6,159,687) (December 12, 2000).

Tsien et al in view of Holzrichter et al. further in view of Foster teach the method of claims 1, 3-9, 15, 17, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. further in view of Foster do not teach the reverse transcriptase as the polymerase.

Vind teaches the reverse transcriptase as the polymerase (Column 7, lines 15-21).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the reverse transcriptase as the polymerase of Vind into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster, since Vind states, "The choice of polymerase is therefore an important means in

controlling the average extension of the primers. These conditions may also exert an influence on the fidelity of the polymerase (the rate by which point mutations are introduced; HIV reverse transcriptase is an example of a polymerase of low fidelity), a parameter useful in combining shuffling and mutagenesis (Column 7, lines 15-21)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the reverse transcriptase as the polymerase of Vind into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster, to improve the function of the DNA polymerase and the sequencing of DNA. An ordinary practitioner would have been motivated to combine and substitute the reverse transcriptase as the polymerase of Vind into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster, in order to achieve the express advantages noted by Vind, of the choice of polymerase which is an important means in controlling the average extension of the primers which also may exert an influence on the fidelity of the polymerase (the rate by which point mutations are introduced; HIV reverse transcriptase is an example of a polymerase of low fidelity), a parameter useful in combining shuffling and mutagenesis.

9. Claim 16 is rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Holzrichter et al. (U.S. Patent 5,620,854) (April 15, 1997) further in view of Foster (U.S. Patent 5,485,277) (January 16, 1996) further in view of Smith et al. (U.S. Patent 5,753,439) (May 19, 1998).

Tsien et al in view of Holzrichter et al. further in view of Foster teach the method of claims 1, 3-9, 15, 17, 21 and 30-34 as described above.

Tsien et al in view of Holzrichter et al. further in view of Foster do not teach the detection of nucleotides by NMR using electromagnetic radiation.

Smith et al. teach the detection of nucleotides by NMR using electromagnetic radiation (Column 7, lines 14-29).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the detection of nucleotides by NMR using electromagnetic radiation of Smith et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster, since Smith et al. state, "These methods can be used to detect characteristic nucleic acid sequences, to determine target sequence and to screen for genetic defects and disorders. Assays can be conducted on solid surfaces allowing for multiple reactions to be conducted in parallel and, if desired, automated (Abstract, last two sentences)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the detection of nucleotides by NMR using electromagnetic radiation of Smith et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster to improve the sequencing of DNA. An ordinary practitioner would have been motivated to combine and substitute the detection of nucleotides by NMR using electromagnetic radiation of Smith et al. into the DNA sequencing method of Tsien et al in view of Holzrichter et al. further in view of Foster in order to achieve the express advantages noted by Smith et al., of the methods which can be used to detect characteristic nucleic acid sequences, to determine target sequence and to screen

for genetic defects and disorders and which can be conducted on solid surfaces allowing for multiple reactions to be conducted in parallel and, if desired, automated.

Response to Amendment

10. In response to amendment, previous 103(a) rejections are hereby withdrawn. However, new 103(a) rejections have been included.

Response to Arguments

11. Applicant's arguments with respect to all pending claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

May 21, 2003

Arun Kr. Chakrabarti

ARUN K. CHAKRABARTI
PATENT EXAMINER